REMARKS

Claims 1-10 and 13-14 are pending in this application. Applicants respectfully request reconsideration of the rejections and objections in view of the following remarks. Claims 1 and 13 have been amended.

Claim 14 has been added. Support for claim 14 can be found in the originally filed claim 13. Thus, no new matter has been added.

In the Office Action, paragraph 1, on page 2, the Examiner stated that "[c]laims 10, 11 have been cancelled. Claims 1-10, and 13 are pending." This appears to be in error. Applicants cancelled claims 11 and 12 in the amendment filed on March 22, 1996. Clarification is requested.

A new Title has been inserted to more clearly indicate the invention to which the claims are directed. Applicants respectfully request that the objection to the Title be withdrawn. (Office Action, ¶ 2.)

Applicants acknowledge the Examiner's withdrawal of the objection to the use of trademarks. (Office Action, ¶ 3, page 2.)

Objection and Rejection Under 35 U.S.C. § 112

Applicants acknowledge the Examiner's withdrawal of the rejection of claims 1-10 under 35 U.S.C. § 112, second paragraph. (Office Action, ¶ 5, page 2.)

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The Examiner maintained the prior rejection of claims 1-10 under 35 U.S.C. § 112, second paragraph, for the recitation of "substantially" and "substantial." (Office Action, ¶ 6, pages 2-3.) Although Applicants previously argued that the terms "substantial" and "substantially" have been accepted by the courts, the Examiner maintained that the phrases are not specifically defined in the specification with regard to a definite level, degree, or range. (Office Action, ¶ 6, page 3.) Applicants respectfully traverse this rejection.

Although claim language such as "substantially" may not be precise, the language does not automatically render the claim indefinite under 35 U.S.C. § 112, second paragraph. (M.P.E.P. § 2173.05(b).) Acceptability of such claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification and in view of the prior art. (M.P.E.P. § 2173.05(b)(d); see also Andrew Corp. v. Gabriel Elec., Inc., 847 F.2d 819, 6 U.S.P.Q.2d 2010 (Fed. Cir.), cert. denied, 488 U.S. 927 (1988).)

Here, the Examiner has not explained why the language "substantially" cannot be reasonably determined by one of ordinary skill in the art from the language of the specification and in view of the prior art. As in In re Marosi, Applicants use the language "substantially" to cover those situations where experimental error exists. (In re Marosi, 710 F.2d 799, 218 U.S.P.Q. 289 (Fed. Cir. 1983) (holding language such as "substantially" or "essentially" may be included in a claim to allow for some

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contamination or experimental error, and does not necessarily render the claim indefinite.) One of ordinary skill in the art would understand that the language "substantially" attempts to define a modified strain of *Shigella*, wherein the *Shigella* cannot substantially invade cells of a host, cannot spread substantially within the infected cells, and cannot produce toxins that will kill substantial numbers of the host's infected, as well as uninfected cells. Applicants respectfully request that the rejection of claims 1-10 under 35 U.S.C. § 112, second paragraph, be withdrawn.

Applicants acknowledge the Examiner's withdrawal of the prior rejection of claims 1-10 and 13 under 35 U.S.C. § 112, first paragraph. (Office Action, ¶ 7, page 3.)

The Examiner maintained the objection to the specification under 35 U.S.C. § 112, first paragraph, as allegedly failing to adequately teach one skilled in the art how to make and/or use the claimed invention. (Office Action, ¶ 8, pages 3-7.) The Examiner argued that the specification fails to provide an enabling disclosure, stating that "construction of claimed *Shigella* mutants requires knowledge of the nucleotide sequence of said genes, which regions are responsible for biological activity, and the number of nucleotides which must be deleted or inserted." (Office Action, ¶ 8, page 4, lines 9-12.) The Examiner continued by stating "[d]ue to the limited teaching of the specification and the unpredictable nature of which mutations are useful one skilled in the art can not practice the invention as claimed absent undue experimentation." (Office Action, ¶ 8, page 4, lines 12-16.) Thus, the Examiner concluded "the only means by

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which applicants can provide an enabling disclosure for the *Shigella* mutants is by depositing said mutants and limiting the claims to the deposited mutants." (Office Action, ¶ 8, page 4, lines 16-19.) In essence, the Examiner is requiring that the claims be limited to only the deposited mutants. Applicants respectfully traverse this rejection.

Applicants respectfully disagree with the Examiner's objection to the specification under 35 U.S.C. § 112, first paragraph, as lacking enablement, and reassert the arguments set forth on pages 5-8 in the response mailed on March 22, 1996. To establish a *prima facie* case of non-enablement, the Examiner must come forward with reasons, supported by the record as a whole, showing why the specification fails to enable one skilled in the art to make and use the claimed invention. The test for enablement is whether one skilled in the art could make or use the invention from the disclosures in the patent *coupled with information known in the art* without undue experimentation. (M.P.E.P. § 2164.01 (italics added).) Moreover, a patent need not teach, and preferably, may omit information well known in the art. (Id.)

The specification describes a method of making a modified strain of *Shigella*, wherein a gene necessary for (1) invasion, (2) spreading, and (3) production of toxins is permanently mutated, by either whole or partial deletions or permanent inactivation. This modified strain can be used to make *Shigella* vaccines.

Applicants respectfully submit that although the specification does not specifically disclose the DNA sequences of genes necessary for invasion and spreading

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of *Shigella*, for example, the iscA, virG, aerobactin, enterochelin, as well as the DNA sequences for the toxin-producing genes, the genomic structure of these genes were well known in the art. Accompanying this response is a PTO 1449 listing references, which disclose the genomic structure for the iscA, virG, and Shiga-toxin genes. Applicants respectfully request that the Examiner consider these references. These references all were available to the public prior to the filing date of the invention. Because a patent may omit information known in the art, it was not necessary for Applicants to include a description of the genomic structure of these genes in the specification in order to enable the claimed invention.

By relying on the specification, one skilled in the art would have known that the exact position of the mutation is irrelevant, as long as the mutation caused permanent inactivation of such genes. (Specification, page 5, lines 8-36, page 6, lines 1-17.) The specification repeatedly requires that the genes necessary for invasion, spreading, and toxin-production, be "wholly or partly removed or permanently inactivated, preferably at least partly removed." (Specification, page 5, lines 26-28, lines 30-34, line 36, page 6, line 1.) The specification also specifically discloses that methods of producing leaky mutations, such as transposon insertions, should not be used:

> [I]t is preferred that the mutagenized genes not be simply inactivated by means of transposons which are inserted into the genes and which can be lost by the genes when they are reproduced in vivo in subsequent Shigella generations when making vaccines of this invention. Rather, the mutagenized genes preferably have had significant portions thereof deleted . . . .

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(Specification, page 6, lines 4-10.) Thus, by referring to the specification, one skilled in the art would have known that *permanent mutations*, and not transposon insertions, in an invasion, a spreading, and a toxin-producing gene were required in order to carry out the claimed invention. Furthermore, claim 1 recites the language "other than only by inactivation by means of a transposon inserted into the genes," distinguishing the claimed invention from the prior art.

One skilled in the art would then have been able to review both the specification and the prior art to identify ways in which to permanently inactivate said genes. For instance, the specification discloses both insertional mutagenesis, and whole or partial deletions, as methods of permanently inactivating the genes. (Specification, Examples 2, 4-7.) Furthermore, other methods of permanently inactivating genes such as the introduction of frameshift mutations, are well known in the art. (See, e.g., Current Protocols of Molecular Biology, Chapter 8, entitled "Mutagenesis of Cloned DNA", for description of ways in which to mutate cloned DNA.) However, by mentioning the above methods as examples of producing permanent mutations, Applicants are in no way excluding other methods of permanent mutations known in the art as of the filing date of the present invention.

Thus, by referring to the specification, one skilled in the art would learn that an effective *Shigella* vaccine could be produced by permanent inactivation of the *Shigella* genes necessary for invasion, spreading, and toxin-production. The specification

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suggests examples of genes involved in invasion, spreading, and toxin-production, and the prior art discloses the genomic structure of these genes. One skilled in the art could then refer either to the specification or to the prior art to determine ways in which to permanently inactivate said genes.

Although some experimentation may be necessary to carry out the claimed invention, Applicants assert that the experimentation would not be undue, but merely routine. (M.P.E.P. § 2164.01.) Thus, as previously asserted on page 7, lines 21-25, of the response filed on March 22, 1996, "[i]n view of the extensive guidance provided by the specification and the background information which is present in the public domain, it is respectfully submitted that the Examiner has failed to establish that practicing the claimed invention would require undue experimentation" and therefore Applicants respectfully request that the objection to the specification under 35 U.S.C. § 112, first paragraph, be withdrawn.

Even though the Examiner requested that the plasmids SC502, SC503, and SC504 be deposited, Applicants respectfully assert that because the specification clearly enables one skilled in the art to make the claimed invention, a deposit of the strains is not required. (M.P.E.P. § 2402.02.)

The Examiner maintained the rejection of claims 1-10 and 13 under 35 U.S.C. § 112, first paragraph, as lacking enablement for the same reasons set forth in the objection to the specification. (Office Action, ¶ 9, page 7.) Applicants traverse this

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rejection and assert the above arguments. Applicants respectfully request that the rejection of claims 1-10 and 13 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejection under 35 U.S.C. § 102

The Examiner maintained the prior rejection of claim 13 under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Sekizaki et al. (Office Action, ¶ 12, page 8.) The Examiner argued that Sekizaki et al. discloses *Shigella* mutants, which lost the ability to produce high levels of Shiga toxin, although the Examiner admitted that Sekizaki et al. did not characterize the *Shigella* mutant. (Office Action, ¶ 12, page 8, lines 34-37.) However, the Examiner concluded that the claimed invention is the "same or an obvious or analogous variant" as the mutant strains described in Sekizaki et al., since both mutant strains allegedly have the same functional properties. (Office Action, ¶ 12, page 8, lines 37-39, page 9, lines 1-3.) In addressing Applicants previous arguments, the Examiner stated that "even if a particular process used to prepare a product is novel and unobvious over the prior art, the product per se, even when limited to the particular process, is unpatentable over the same product taught by the prior art." (Office Action, ¶ 12, page 10, lines 1-4.) Applicants respectfully traverse this rejection.

Applicants respectfully disagree with the Examiner's rejection of claim 13 under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as

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obvious over Sekizaki et al. Applicants reassert the arguments set forth on pages 8-9 in the response mailed March 22, 1996. In clarifying Applicants' previous assertions, Applicants were not arguing that using a particular process to prepare the *Shigella* mutants necessarily made the product patentable over the prior art. Instead, Applicants asserted that the process disclosed in the specification produced mutant *Shigella* having the benefit of lacking the potential to revert to virulent *Shigella*. This lack of reversion aids in the production of a vaccine that can be safely used to protect individuals against bacillary dysentery.

Applicants have amended claim 13 to recite the language "other than only by inactivation by means of a transposon inserted into the genes." Support for this language can be found on page 6, lines 4-6. By adding this phrase, Applicants clearly distinguish the claimed invention from the "leaky" transposon insertion mutants disclosed in Sekizaki et al. Applicants assert that Sekizaki et al. fails to suggest the claimed invention, and thus, Applicants respectfully request that the rejection of claim 13 under 35 U.S.C. § 102, or in the alternative under 35 U.S.C. § 103, be withdrawn.

Rejection under 35 U.S.C. § 103

The Examiner maintained the prior rejection of claims 1-10 under 35 U.S.C.

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§ 103 as being unpatentable over Mills et al. in view of Sekizaki et al., Nassif et al., Makino et al., and Ozenberger et al. (Office Action, ¶ 13, page 10.) After considering Applicants previous argument that the cited prior art lacks motivation to combine, the Examiner alleged "[i]t is the Examiner's position that there is motivation to combine . . . [because] VirG and aerobactin are useful in a vaccine (see Nassif et al. and Makino et al.), aerobactin mutant provides additional security for sufficient attenuation in a vaccine (see Mills et al. and Nassif et al.), [and] Mills et al. teaches the potential for reversion to virulence represent possible problems." (Office Action, ¶ 13, page 11, lines 27-31, page 12, lines 1-2.) Applicants respectfully traverse this rejection.

Applicants respectfully disagree with the rejection of claims 1-10 under 35 U.S.C. § 103 as being unpatentable over Mills et al. in view of Sekizaki et al., Nassif et al., Makino et al., and Ozenberger et al. Applicants reassert the arguments made on pages 9-11 in the response mailed March 22, 1996. Applicants also submit the following comments.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. (See M.P.E.P. § 2142.)

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As described on pages 6-7 of this response, the claimed invention relates to a method of making a modified strain of *Shigella* having permanent mutations in a gene necessary for (1) invasion, (2) spreading, and (3) toxin-production. This modified strain can then be used to make a *Shigella* vaccine. Furthermore, independent claim 1 recites the language "other than only by inactivation by means of a transposon inserted into the genes." None of the cited references alone, or when combined, teach the claimed invention.

First, as explained on pages 7-9 of this response, the specification discloses the importance of permanently inactivating the genes necessary for invasion, spreading, and toxin-production in order to make a nonvirulent vaccine. (Specification, page 5, lines 18-36, and page 6, lines 1-17.) The specification specifically states that methods leading to the production of leaky mutations in genes, such as transposon insertions, should be avoided because these mutations are likely to spontaneously revert. (Id.) If spontaneous reversion occurs, and these strains are used to produce *Shigella* vaccines, a vaccinated individual is likely to develop full-blown dysentery.

However, all of the cited references that suggest using *Shigella* mutants as vaccines (Sekizaki et al., page 2213, last paragraph, Nassif et al., page 1968, last paragraph, Makino et al., page 554, first column, first full paragraph, and Mills et al., Abstract) rely on transposon insertions to produce the mutations in the *Shigella* genome. For example, the Abstract of Sekizaki et al. reports that *Shiga*-toxin mutants

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were generated by "in vivo insertion mutagenesis with a Tn10 derivative transposon." Similarly, the Abstract of Nassif et al. describes the production of an aerobactin mutant generated with "Tn10 insertion." The Experimental Procedures section of Makino et al. states "[s]eventeen Tn5 insertion mutants" were isolated of the virG gene. Finally, Figure 4 of Mills et al. illustrates the procedure used in isolating mutants using transposon insertions.

Thus, these cited references teach away from the claimed invention because one of ordinary skill in the art, relying on these references, would have used transposon insertions to mutate the *Shigella* genes. The cited references therefore fail to suggest the claimed invention.

Second, the claimed invention specifically requires mutations in the toxin-producing genes, as well as the genes necessary for the invasion *and* the spreading of *Shigella*. However, all cited references detailing vaccines against *Shigella* (Mills et al., Makino et al., Sekizaki et al., and Nassif et al.) specifically maintain wild-type function of the invasion and spreading genes.

For instance, Mills et al., page 120, second column, describes the generation of "attenuated derivatives of *S. dysenteriae* 1 that are non-pathogenic but retain the capacity to colonize and *invade* the intestinal mucosa." Similarly, the authors of Makino et al., page 554, first column, second paragraph, explain their results, stating "[t]his suggests that the Tn5 insertions mutants used in this study may *invade* colonic epithelia

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and multiply therein but are presumably unable to induce dysentery." Furthermore, Sekizaki et al., page 2213, last paragraph, states that "[o]ne group of live-vaccine candidates under development are aromatic amino acid-dependent (Aro$^-$) *Shigella* mutants that retain their *invasive* properties but whose metabolic lesions render them nonpathogenic."

Finally, in the second to last paragraph of Nassif et al., the authors hypothesize that the function of the aerobactin gene, as evidenced by their data, suggests that "aerobactin production operates at the stage of multiplication within tissues when bacteria lie within the extracellular compartment of the intestinal villus. Such a mutant may be worth considering as a component of a vaccine." In other words, the authors of Nassif et al. do not consider genes necessary for invasion or spreading of *Shigella* as components of vaccine, but genes involved in the multiplication within tissues. Clearly, none of these references, Mills, Nassif, Sekizaki, or Makino, render obvious the claimed invention, since none of these references teach permanent inactivation of the (1) invasion, (2) spreading, and (3) the toxin-producing genes.

The final reference cited by the Examiner, Ozenberger et al., also fails to suggest the claimed invention. Ozenberger et al. describes mutations in a bacterial transport gene of *E. coli,* the enterobactin gene. Ozenberger et al. does not describe mutations in the enterobactin gene of *Shigella,* or even mutations in an enterobactin gene of an

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enteroinvasive strain of *E. coli.* Without more, Ozenberger et al. fails to suggest mutations in the enterobactin gene of *Shigella*.

Furthermore, there is no motivation to combine Ozenberger et al. with the other cited references. At no point does Ozenberger et al. suggest that the enterobactin gene of *E. coli* is at all related to the enterobactin gene of *Shigella*. In fact, Mills et al. suggests that the genes between the species *Shigella* and enteroinvasive *E. Coli*, as well as between strains of *Shigella* may be dissimilar:

> Although it is likely that a similar constellation of pathogenicity factors are responsible for the virulence of all shigellae and [enteroinvasive E. coli], there are some interesting genetic differences among the species (in order of decreasing virulence: *S. dysenteriae* 1, other serotypes of *S. dysenteriae* and *S. flexneri*, *S. sonnei*, enteroinvasive E. coli), as well as interstrain variation.

(Mills et al. page 118, second column, third paragraph.) Clearly, Mills et al. teaches away from equating the enterobactin gene of a non-enteroinvasive strain of *E. coli,* as described in Ozenberger et al., to the enterobactin gene of *Shigella*, since Mills et al. reports that not only are the genomes of different strains of *Shigella* dissimilar, so are the genomes of *Shigella* as compared to the genome of an enteroinvasive strain of *E. coli.* Thus, there exists no evidence of motivation to combine Ozenberger et al. with Mills et al., Makino et al., Sekizaki et al., and Nassif et al.

In summary, a *prima facie* case of obviousness has not been made, since Mills et al., Sekizaki et al., Nassif et al., and Makino et al. all fail to suggest permanent mutations in the genes necessary for invasion, spreading, and toxin-production. All of

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these references suggest using mutant strains of *Shigella* produced by leaky transposon insertions, which have maintained wild type function of the invasion and the spreading genes. The last reference, Ozenberger et al. fails to supply the missing information, since this reference describes mutations in a gene from a microorganism other than *Shigella*.

For all of these reasons, Applicants respectfully request that the rejection of claims 1-10 under 35 U.S.C. § 103 as being unpatentable over Mills et al. in view of Sekizaki et al., Nassif et al., Makino et al., and Ozenberger et al. be withdrawn.

Applicants note that the Examiner maintained the provisional rejection of claim 13 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 39 of copending application Serial No. 08/118,100. (Office Action, ¶ 14, page 12.)

Applicants again respectfully request that the Examiner hold this provisional rejection in abeyance until allowable subject matter has been indicated.

New Grounds of Rejection

The Examiner provisionally rejected claims 1-10 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 36, 37, 38, and 40 of copending application Serial No. 08/118,100. (Office Action, ¶ 15, page 12.) The Examiner argued that although the allegedly conflicting claims are not

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identical, the claims are not patentably distinct from each other because both are drawn to *Shigella* mutants which have an inactivated gene encoding *Shiga*-toxin, aerobactin, enterochelin, and iscA. (Office Action, ¶ 15, page 12, lines 28-31, page 13, lines 1-2.)

Applicants respectfully request that the Examiner hold this provisional rejection in abeyance until allowable subject matter has been indicated in either of the applications.

Conclusions

In view of the foregoing remarks, Applicants believe that this application is now in condition for allowance.

If any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this amendment, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. § 1.16 or §1.17 which are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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By: _____
Kenneth J. Meyers
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Dated: December 20, 1996
KJM/MMW/clw

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